REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim 1 has been amended as suggested by the Examiner. Claim 1 is further amended to incorporate the limitations of claims 4 and 7. Claims 4, 7 and 8 are cancelled without prejudice. Claim 5 has been amended as suggested by the Examiner. The amendments to claim 1 are further supported in the specification at page 10, line 5 from the bottom of the page to page 11, line 6.

In view of the foregoing amendments, the rejection of claims 4, 5 and 7 under 35 USC 112, second paragraph, is deemed to be overcome.

Claims 1-6 and 8 were rejected under 35 USC 102 as being anticipated by EPO '704, and separately, JP '424. Claims 1-6 are further rejected under 35 USC 102 as being anticipated by JP '955.

Each of the foregoing grounds of rejection are deemed to be overcome in view of the foregoing amendments.

Reference EPO '704 discloses a glycyrrhizin suppository for absorption, but does not disclose any oral preparation for the transmucosal absorption in the large intestine of the present invention. The amended claim 1 is restricted to the oral preparation in the form of capsule wherein the drug is released in the large intestine by the collapse of the capsule by internal pressure.

Reference JP '424 discloses a cream for transdermal absorption and JP '955 discloses an eye drop preparation, unlike the special oral preparation of the present invention.

In view of the foregoing, these grounds of rejection are deemed to be overcome.

Lastly, claims 1-8 are rejected under 35 USC 103 as being unpatentable over JP '731 in view of WO '622. This ground of rejection is also deemed to be overcome in view of the foregoing amendments to the claims.

Reference JP '731 discloses a glycyrrhizin suppository for rectal administration, but does not disclose any oral preparation containing the mixed ester of the present invention as claimed in

the amended claim 1 wherein the capsule releases the drug in the large intestine by the collapse of the capsule by internal pressure.

Reference WO '622 discloses calcitonin preparations containing glycyrrhizin (GZ) and Labrasol® in the ratio of 5.0 to 400.0 (in Example 11), and 5.0 to 500.0 (in Example 24), but does not disclose a preparation containing the specific ratio of GZ to the ester mixture claimed in the amended claim 1 of the present invention.

Nor does WO '622 disclose any experimental data which would allow one skilled in the art to estimate the effectiveness of a polyglycolysed glyceride such as Labrasol in achieving an effective plasmid concentration of glycyrrhizin by oral administration. As recognized by the Examiner, WO '622 is directed to improving the absorption of a calcitonin. Only two experimental examples are described in the cited reference, and these examples show administration of preparations rectally and intracolonically. Neither of the preparations contained glycyrrhizin, and both examples only measured residual serum calcium concentrations with and without Labrasol.

Glycyrrhizin is a major effective component of licorice, and is known to have many actions such as anti-allergic action, anti-inflammatory action, antiviral action and steroid-like action, and it is important as a medicine for treating chronic hepatic diseases. When glycyrrhizin is administered intravenously as an injection, the therapeutic action appears significantly. However, when it is orally administered, the therapeutic action is not clearly shown because of its poor absorption via digestive tracts.

Further, when glycyrrhizin is orally administered, it is hydrolyzed by enterobacteria present on the digestive mucosae to release its sugar moiety, and thus absorbed as glycyrrhetic acid, but the pharmaceutical activity of glycyrrhetic acid against hepatitis is considerably lower than that of glycyrrhizin.

To improve the bioavailability of glycyrrhizin, intra-rectal administration thereof in the form of suppositories has been proposed.

For improving absorption via digestive tracts, an oral preparation blended with a fatty acid glyceride and coated with an enteric polymer and an oral preparation blended with a fat emulsion

or a complex lipid mixture have also been proposed. However, these conventional suppositories and oral preparations could not achieve blood glycyrrhizin concentrations enough to demonstrate the efficacy thereof.

Administration by injection not only gives a sharp pain to the patient but also has to be performed only by a doctor for each administration. Accordingly, administration by injection to a patient particularly having a chronic disease results in considerable mental and physical pain.

As a result of extensive study for solving the problem described above, the present inventors found that when glycyrrhizin is dissolved or dispersed in a self-emulsifying agent comprising an ester mixture of a C_{6-18} fatty acid glycerol ester with a C_{6-18} fatty acid macrogol ester and then administered to the digestive tract, glycyrrhizin which has hardly achieved a sufficient blood concentration upon administration by the conventional oral preparations or suppositories can be well absorbed, particularly via colon mucosae, to achieve a blood concentration effective for treating chronic hepatic diseases.

The glycyrrhizin oral preparation in a form of a capsule for transmucosal absorption according to the present invention shows a high level plasma concentration of glycyrrhizin. See Table 2, Examples 1 to 4, and Table 4, Example 6, on pages 13-15 of the specification.

Even if one skilled in the art would have been motivated by the combined teachings of the cited references to combine glycyrrhizin and the mixed ester of the present invention in an oral preparation, one skilled in the art could not have had a reasonable expectation that the claimed preparation in the specified weight ratio would achieve the high level plasmid concentration of glycyrrhizin as demonstrated in the specification.

Accordingly, it is respectfully submitted that the claimed invention would have been nonobvious from the combined teachings of the cited references.

Accordingly, reconsideration and allowance is respectfully solicited.

Respectfully submitted,

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